Applicants : LOUVEL, Pascal Claude Michel, et al.

Title : MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME

The following documents are submitted for the above-identified invention for entry into the U.S. National stage under 35 U.S.C. §371, based on the International Application No. PCT/FR98/00697, which includes the following:

1. Three (3) pages of Transmittal Letter to the United States Elected Office (EO/US);

2. Calculation sheet, in duplicate

3. Cover sheet of International Publication No. WO 98/44911

4. English translation of International Publication No. WO 98/449, including Abstract and amended pages 2 and 2a.

5. One sheet of formal drawing

6. Return Receipt Post Card

"Express Mail" Mailing Label No. EL 345 324 971 US
Date of Deposit 06 October 1999

I hereby certify that the above-identified documents are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR I.I0 on the date indicated above and is addressed to BOX PCT, Assistant Commissioner for Patents Washington, D.C. 2023I, Attention RO/EO/US

Andre' Steed

Andre Steed

Attny Docket No. P1047/20008

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

International Application No.	:	PCT/FR98/00697
International Filing Date	:	07 April 1998
Priority Date Claimed	:	07 April 1997
Title of Invention	:	MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME
Applicant(s) for DO/EO/US	:	LOUVEL, Pascal Claude Michel RAGOT, Francoise CLEE, Marie-Christine CHAUVEAU, Charles

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Attention: EO/US

Sir:

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

3. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

4. A copy of the International Application as filed (35 U.S.C 371(c)(2)) has been transmitted by the International Bureau. A copy of the cover sheet of the international application, International Publication No. WO 98/44911 is attached hereto.

5. A copy of an English translation of International Publication No. WO 98/449, including Abstract and amended pages 2 and 2a.

7. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(1)(1)-(5):

	For	Number Filed	Number Extra	Rate	Calculation
Claims Fee	Total Claims	4	0	x 18	
	Independent Claims	3	0	x 78	
	Multiple Dependent Claims			x260	
Basic Fee	U.S. PTO was not International Preliminary Examination Authority. Search report on the international application was prepared by the European Patent Office				$ 840
	Total of above Calculations				$ 840
	Reduction by ½ for filing by small entity				$
	Subtotal				$
	TOTAL NATIONAL FEE				**$ 840**

Please charge counsel's account no. 03-0075 in the amount of $840, or any additional amount which may be required, to cover the above fees. A duplicate copy of the calculation sheet is enclosed.

AUTHORIZATION TO CHARGE ADDITIONAL FEES

The Commissioner is hereby authorized to charge the following additional fees which may be required by this paper and during the entire pendency of this application to counsel's deposit account no. 03-0075:

1. 37 CFR 1.492(a)(1), (2), (3) and (4) (filing fees)

2. 37 CFR 1.492(b), (c) and (d) (presentation of extra claims)

3. 37 CFR 1.17 (application processing fees)

4. 37 CFR 1.492(e) and (f) (surcharge fee for filing declaration and/or filing an English translation of an International Application later than 30 months after the priority date)

This application and items attached are being transmitted before the 30 month claimed priority date.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

October 6, 1999

By_____

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MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME

The invention consists in a multiparticulate pharmaceutical form, in particular a multiparticulate tablet of the kind based on a plurality of individual particles obtained by hot extrusion and individually containing the active material.

It is also directed to a new industrial product consisting of the particles constituting said multiparticulate pharmaceutical form.

It is further directed to a method and plant for preparing said constituent particles.

Solid pharmaceutical forms prepared from a molten mixture without solvents of active substances and thermoplastics material are disclosed in patent US-A-3 432 592, for example, in which they are shaped by injection moulding, and patent EP-A-0 190 255, in which the molten mass is either injection moulded or extruded.

Documents WO-A-9614058 and WO-A-9614059 disclose tablets of the kind in question which are prepared by compressing a set of individual particles consisting of a thermoplastics material matrix within which an active substance is dispersed, the particles being obtained by chopping the filament leaving the die of an extruding machine inside which the mixture of the thermoplastics material and the active substance has previously been subjected to the conditions of hot extrusion; note that before the compression step the particles obtained at the exit from the die can be subjected to a spheroidal shaping to give them rounded contours.

The major drawback of the above tablets is their low rate of disintegration, which makes it very difficult to disperse the individual particles within the digestive tract.

Also, document EP-A-0 548 356 describes tablets of the kind in question prepared by compressing a mixture containing individual particles obtained by extrusion and spheroidal shaping of an active substance and having a coating to mask the taste and an excipient based on at least one disintegrating agent and/or at least one swelling agent.

The tablets are distinguished by a very high rate of disintegration, leading to dispersion of the individual particles in the mouth, which is rendered acceptable by the presence of their coating.

Finally:

- document DE-A-44 13 350 discloses tablets based on particles obtained by hot extrusion from a mixture of an active substance and a polymer, chopping the extruded filament and shaping the particles, which are optionally coated with a polyacrylate or a cellulose ester, and

- document DE-A-41 22 217 discloses tablets based on particles obtained by wet cold extrusion from a mixture of polymers and active substance, followed by spheroidal shaping and coating.

The most important object of the invention is to provide a multiparticulate pharmaceutical form, in particular a multiparticulate tablet of the kind in question, which has a rate of disintegration such that its disintegration and consequently the dispersion of the individual constituent particles occur in less than 15 minutes in a standard disintegration measuring device, in other words in the upper part of the digestive tract.

Through in-depth research, the applicant company has found that the above object is achieved if the individual particles constituting said multiparticulate pharmaceutical form have a coating based on at least one binding agent, at least one disintegrating agent and optionally at least one active principle.

It follows that the multiparticulate pharmaceutical form in accordance with the invention is characterised in that it consists of a plurality of particles, preferably spheroids having a coating based on at least one disintegrating agent and at least one binding agent and optionally at least one active substance and consolidated with one another by compression, said particles or spheroids in which an active substance is distributed within a thermoplastics material having been obtained by hot extrusion without solvent of a mixture of the active

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substance with the thermoplastics material and chopping the filament or extrudate leaving the extrusion die.

The particles, preferably the spheroids in accordance with the invention, constituting the multiparticulate pharmaceutical form of the invention are characterised in that they are the result of chopping a filament or extrudate obtained by hot extrusion without a solvent of a mixture of an active substance and a thermoplastics material and coating the particles obtained by chopping with a coating including at least one binding agent and at least one disintegrating agent.

It is by virtue of the progressive extraction of the active material from the matrix consisting of the thermoplastics material - which causes the active substance to pass into the surrounding medium - that the multiparticulate pharmaceutical forms, in particular the multiparticulate tablets of the invention constitute a pharmaceutical form with modified and controlled release.

The curve of the *in vitro* release expressed as a percentage of the active substance as a function of time is a predetermined essential characteristic of the pharmaceutical form and must be reproduced from one tablet to another.

It is the result of a judicious choice of the constituent characteristics of the matrix.

In the case of preparing individual particles included in the multiparticulate pharmaceutical form, in particular the multiparticulate tablet, by extruding the mixture of an active substance and a thermoplastics material constituting the matrix and by chopping the extruded filament at the exit from the die, it is important for the extrusion to be carried out less than 6 hours at 25°C after the mixture to be extruded is made up, at risk of obtaining particles and consequently tablets for which the curve showing the release of the

active substance as a function of time is modified in the sense of a reduced percentage of active substance released per unit time.

This constraint, which is not referred to in the prior art, constitutes a major drawback in that if a mixture ready to be extruded had to be stored for whatever reason for a time exceeding the above limit before it could be extruded, the mixture would have to be regarded as wasted because of the inevitable deterioration of the curve showing the release of the active substance from the particles obtained by extrusion.

The applicant company has found that it is possible to overcome this drawback by subjecting the mixture of the active substance and the thermoplastics material to a maturing step.

When said mixture is subjected to this maturing step - whose duration is from 30 minutes to 150 hours at a temperature in the range from 20°C to 70°C - its extrusion yields particles which have an active principle release curve which is stabilised provided that the time lapse between the preparation of the mixture and its extrusion does not exceed approximately 7 days.

It is found that this - stabilised - active principle release curve represents slower kinetics than are obtained with particles with the same composition but extruded immediately after making up the mixture, with no maturing step; this means that at a given time the percentage of active substance released by the particles prepared by extrusion after maturing is less than that released by particles extruded without maturing.

For the two curves to be superposed, the mixture subjected to a maturing step before extrusion must contain a greater concentration of active substance.

The maturing phase therefore has an additional

advantage in that the particles obtained by the method of the invention including the maturing phase introduce into the organism an increased quantity of active substance for the same volume or even a reduced volume and at an equivalent rate.

It follows that the method in accordance with the invention of making particles, in particular spheroids with a constant diameter in the range from 0.5 mm to 2 mm, including an active substance and having a controlled and predetermined active substance release curve, which method includes successively:

- a step of selecting an active substance and a thermoplastics material, including at least one polymer excipient and at least one plasticiser,
- a step of mixing the active substance and the thermoplastics material,
- a step of extruding the mixture without solvent at a controlled temperature to produce at least one extruded filament or extrudate, and
- a step of chopping the extrudate into particles,

is characterised in that it includes a step of maturing the mixture of the active substance and the thermoplastics material before extrusion at a temperature and for a time chosen according to the characteristics of the intended active principle release curve and respectively in the range from 20°C to 70°C and in the range from 30 minutes to 150 hours, whereby it becomes possible to store the mixture of the active substance and the thermoplastics material for up to 7 days before extruding it and to increase the quantity of active substance for a given release curve without increasing the volume of the tablet.

As a result of this, the particles constituting the multiparticulate pharmaceutical form, in particular the multiparticulate tablet of the invention, are preferably

in the form of spheroids, i.e. have rounded contours.

The spheroidal shaping constitutes an additional process step generating an additional cost; moreover, it is possible only if the extrudate retains physical properties such that it can be formed to a spheroidal shape at the working temperature.

The applicant company has found that it is possible to obtain the particles in accordance with the invention directly in spheroidal form at the exit from the die provided that the cutters in the chopping device at the exit from the die have the shape described later and shown in figures 1 and 2.

It follows that the plant of the invention for making spheroids in accordance with the invention comprises an extruding machine having a tool for chopping the extruded filament or extrudate at the exit from the extrusion die fitted with cutters having the shape shown in figures 1 and 2.

The invention will be better understood with the aid of the additional description that follows and the non-limiting examples which concern advantageous embodiments of the invention.

Consequently, the following process or an equivalent process is used to make the particles, in particular the spheroids, in accordance with the invention and the multiparticulate pharmaceutical form, in particular the multiparticulate tablet containing them.

First an active substance and the constituents of a thermoplastics material, namely at least one polymer and at least one plasticiser, are selected.

The active substance, which must be stable from the physical point of view and from the chemical point of view at the softening point of the thermoplastics material, is advantageously chosen from the group comprising gastrointestinal sedatives, antacids,

analgesics, anti-inflammatories, coronary vasodilators, peripheral and cerebral vasodilators, anti-infective agents, antibiotics, antiviral agents, antiparasitic agents, anti-cancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrhoeal agents, laxatives, food supplements, immunosupressors, cholesterol-lowering agents, hormones, enzymes, antispasmodics, antianginals, drugs influencing cardiac rhythm, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs influencing the coagulation of blood, antiepileptics, muscle relaxants, drugs used in the treatment of diabetes, drugs used in the treatment of thyroid dysfunction, diuretics, anti-anorexia agents, anti-asthmatic agents, expectorants, antitussives, mucoregulators, decongestants, hypnotics, anti-emetics, haematopoietics, uricosurics, plant extracts, contrast agents.

Its particle size range must be compatible with homogeneous dispersion within the thermoplastics material.

Its particle size range is advantageously from 0.1 μm to 500 μm and preferably from 1 μm to 100 μm.

The polymer is a thermoplastics polymer whose softening point is preferably in the range from 10°C to 50°C below the melting point of the active substance; it is advantageously chosen from the group comprising ethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetosuccinate, cellulose acetobutyrate, cellulose acetopropionate, cellulose acetophthalate, hydroxypropylmethyl cellulose phthalate, microcrystalline cellulose, sodium carboxymethyl cellulose, polymethacrylate, polyethylene oxides, polyvinyl pyrrolidones, cross-linked starch, lactic acid,

polyvinyl acetate, polyvinyl alcohol and vinyl acetate resins.

It is advantageously in the form of a powder.

The plasticiser is preferably chosen from those which are liquids and more particularly from the group comprising ethyl phthalate, dibutyl sebacate, triacetine, triethyl citrate, dioctyl phthalate, diphenyl phthalate, dibutyl phthalate, polyethylene glycol and acetylated monoglycerides.

The active substance and thermoplastics polymer powders are mixed and the plasticiser is incorporated into the mixture.

A planetary mixer can be used to perform the mixing or preferably a double-jacket fast shear type mixer.

Collette mixers can be used.

The temperature of the constituents of the mixture during the mixing operation is in the range from 20°C to 70°C.

The respective proportions of the active substance, the polymer and the plasticiser are preferably as follows:

- active substance: 5 wt% to 80 wt%,
- polymer: 5 wt% to 80 wt%, and
- plasticiser: 1 wt% to 25 wt%.

The mixture advantageously includes from 0.1 wt% to 1 wt% colouring agent.

The mixture obtained as described above is subjected to an extrusion operation.

However, in accordance with the invention, it is first subjected to a maturing step.

The maturing step consists in maintaining the mixture at a temperature in the range from 20°C to 70°C, preferably in the range from 35°C to 70°C, for 30 minutes to 150 hours, advantageously in a ventilated tray type oven.

The duration of the maturing step can be reduced to less than 10 hours provided that the mixture is agitated slowly in the mixer during the maturation step.

Because of the maturing step, the mixture consisting of the thermoplastics material and the active substance can be stored for up to 7 days before the extrusion step.

The extrusion step is carried out in an extruding machine, for example a single-screw machine, into whose kneading area the mixture is introduced in powder form.

In the kneading area, the mixture is subjected to the following temperature and pressure conditions:

- temperature: from 20°C to 200°C, and
- pressure: from 10 bars to 160 bars.

It remains in the kneading area for 2 to 6 minutes.

The temperature, pressure and duration parameters are chosen according to the characteristics of the polymer in the mixture and the size of the spheroids to be obtained.

Because of the conditions that apply in the kneading area, the original powder mixture is converted into a fluid paste in which the particles of active substance remain in the solid state.

The fluid paste is extruded through a die whose diameter depends on the required size of the spheroids and is in the range from 0.5 mm to 2.0 mm.

At the exit from the die, the extruded mixture is in the form of a filament or an extrudate whose diameter exceeds the diameter of the die by 20% to 150% because of expansion; the filament or extrudate is solidified and stiffened by cooling, for example using a jet of air.

It is possible to use a multiple die that produces a plurality of filaments or extrudates.

The filament exit rate is from 10 to 80 g/minute and depends on the rotation speed of the screw.

The filament or extrudate obtained at the exit from

the die is chopped by a rotary chopping tool comprising one or more cutters; the chopping tool is disposed so that the distance between the face of the die across which the cutters are moved by the rotation of the tool and the surface of said cutters is from 0.04 mm to 0.15 mm.

According to the invention, the cutters have the shape shown in figures 1 and 2.

Figure 1 is a plan view of a cutter C in accordance with the invention and figure 2 is an end view of it as seen in the direction of the arrow II-II in figure 1.

As shown in figure 1, the cutter C, which is generally rectangular with two longer sides m_1 and m_2 and two shorter sides n_1 and n_2, has:

- a solid part C_1 by means of which it is fixed to the chopping tool, not shown, for example by screws, not shown, for which two threaded holes T_1 and T_2 are provided, and
- a part C_2 which is recessed from the longer side m_2 towards the longer side m_1 which includes the cutting edge T of the cutter, to a distance d from the side m_1 which is less than 1 mm, so that the surface of the cutter consisting of the face shown of the part C_1 is extended along the side m_1 in the part C_2 by a strip B of width d.

Figure 2 shows clearly the recessed shape of the part C_2, the cutting edge on the side m_1 and the strip B of width d.

The arrow F_1 in figure 1 shows the direction the cutters move when the chopping tool rotates.

Accordingly, as the chopping tool rotates, the cutting edges T of the cutters C impinge on the filament, not shown, leaving the die, not shown, and chop the filament into successive particles.

It is because, in accordance with the invention, the

width of the strip B is less than 1 mm that chopping the filament or extrudate leaving the die produces particles of spheroidal shape directly, with no additional spheroidal shaping step, the precise value of d being determined by the diameter of the hole in the die and the rate at which the extruded filament leaves it.

The relationship between the value of d, the diameter of the hole in the die and the exit rate of the extrudate is determined empirically in each individual case.

The greatest dimension of the spheroidal particles obtained is generally in the range from 0.5 mm to 2 mm.

This dimension is a function of the rotation speed of the extrusion screw shaft, the temperature gradient in the extrusion area, and the temperature and dimensions of the die. The rotation speed of the screw shaft is preferably in the range from 1 rpm to 90 rpm. The temperature gradient in the extrusion area and the temperature of the die are preferably in the range from 20°C to 200°C. The diameter of the die orifice is preferably in the range from 0.5 mm to 2 mm.

The rotation speed of the chopping tool is fixed by the rate at which the extruded filament leaves the die orifice and is preferably in the range from 40 rpm to 1 500 rpm.

The spheroidal particles obtained at the exit from the die are coated with a coating including at least one disintegrating agent; the coating can also include a binding agent; it can further contain an active substance.

A turbine or a fluidised air bed can be used for this purpose.

Firstly, the binding agent is sprayed on in the form of a 10 wt% to 30 wt% solution in an appropriate and pharmaceutically acceptable solvent, preferably alcohol

or water. From 1 wt% to 50 wt% of disintegrating agent relative to the weight of the spheroids is then fixed in the powder state to the spheroids covered with binding solution.

The spheroidal shape of the particles is essential for obtaining effective coating.

The particle size range of the disintegrating agent is preferably from 1 µm to 100 µm.

The disintegrating agent is chosen from the group comprising cross-linked polyvinyl pyrrolidone, modified starch and cross-linked sodium carboxymethyl cellulose, and the binding agent is preferably chosen from the group comprising polyvinyl pyrrolidone, polyethylene glycol, polymethacrylate and hydroxypropylmethyl cellulose.

The total mass of the coating is preferably 2 wt% to 20 wt% relative to the mass of the spheroidal particles.

The multiparticulate pharmaceutical form, in particular the multiparticulate tablet, according to the invention, is prepared from the spheroids obtained in the above way.

Compression techniques familiar to the skilled person can be used for this purpose.

The parameters of the compression step are set so that the hardness of the resulting tablets is in the range from 30 N to 70 N.

EXAMPLE 1

This example concerns spheroids containing sodium diclofenac as the active substance.

It includes an assessment of the effect of the maturing step on the rate of release of the active substance from the spheroids.

The polymer chosen for constituting the thermoplastics material is a polymer of ethyl cellulose having a softening point of 130-133°C (glass transition temperature).

It is not soluble in an aqueous medium, or only slightly soluble, and the viscosity of a 5% (m/m) alcohol solution of the polymer at 25°C is from 5 mPa to 8 mPa. This polymer is sold under the name EC N7NF by Aqualon/Hercules.

The plasticiser used was diethyl phthalate.

Hereinafter, the active substance, the polymer and the plasticiser are designated by the following abbreviations:

- DFC: sodium diclofenac,
- EC N7NF: ethyl cellulose polymer, and
- DEP: diethyl phthalate.

The centesimal composition of the mixture for preparing the spheroids was as follows:

- DFC: 25 wt%,
- EC N7NF: 65 wt%, and
- DEP: 10 wt%.

To assess the effect of the maturing step on the curve showing release of the active substance from spheroids obtained by extruding the above mixture, nine samples A1, A2, B1, B2, B3, B4, C1, C2 and C3 of the mixture were prepared.

Samples A1 and A2 were maintained at room temperature for four hours and two days, respectively, before extrusion.

Samples B1 through B4 were subjected to a maturing step at 70°C in an oven for four hours, one day, two days and three days, respectively.

Samples C1 through C3 were subjected to a maturing step at 40°C in an oven for one day, two days and three days, respectively.

The nine samples were extruded using a single-screw extruding machine and then chopped, the extrusion parameters being as follows:

- temperature in the extrusion area: 130°C to 170°C,

- screw speed: from 20 rpm to 75 rpm,
- pressure in the extrusion area: from 25 bars to 130 bars, and
- die orifice diameter: 1 mm.

The extruded filament or extrudate was chopped using a chopping tool with cutters in accordance with the invention, the rotation speed of the chopping tool being adjusted to obtain the best possible hot spheroidal shaping. This speed was 756 rpm, for example.

The particle size range of the spheroids obtained was from 1.2 mm to 1.6 mm.

Using measuring apparatus designated 'Apparatus I' in the American Pharmacopoeia (USP XXIII) and 'Rack apparatus' in the European Pharmacopoeia (3rd edition), the conditions of use of the apparatus being 1 litre of pH 7.0 buffer solution at 37°C per reactor and a rotation speed of 100 rpm, the percentages of active substance released *in vitro* after 0.5 hour, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours and 8 hours were determined for the spheroids obtained from each of samples A1 through C3 processed as indicated above.

The values obtained are set out in Table I.

TABLE I

H	Percentage of active substance released in the case of the samples								
	A1	A2	B1	B2	B3	B4	C1	C2	C3
0.5 hour	31.5	29.6	12.4	8.8	6.0	4.7	17.7	10.6	9.1
1 hour	44.1	41.1	22.9	20.2	12.7	9.7	30.6	19.8	17.8
1.5 hours	53.2	50.8	31.7	32.3	21.3	16.9	41.9	28.1	26.1
2 hours	62.8	57.4	39.4	41.6	29.4	23.9	49.7	35.6	32.6
3 hours	72.8	63.5	54.5	59.0	42.6	36.3	62.9	49.9	44.9
4 hours	77.1	74.5	63.3	68.4	54.2	47.5	70.1	57.7	55.0
5 hours	82.7	79.4	69.8	74.1	61.5	55.7	73.1	64.9	61.1
6 hours	85.6	82.3	71.9	75.5	66.9	62.0	76.1	69.0	66.5
7 hours	87.3	85.5	74.7	77.2	71.7	66.2	80.3	72.5	70.2
8 hours	86.5	85.1	76.2	78.7	72.9	69.5	80.4	75.2	72.5

Column H shows the measurement time relative to the start of the experiment.

The conclusion that can be drawn from the values set out in the table is that the maturing treatment slows the kinetics of dissolving the active substance.

EXAMPLE 2

This example shows how the maturing step stabilises the curve showing release or dissolution of the active principle from spheroids when the matured mixture was stored before it was extruded, the mixture being the same as that described in example 1, i.e. a mixture comprising:

- DFC: 25 wt%,
- EC N7NF 65 wt%, and
- DEP: 10 wt%.

Three samples D1, D2 and D3 were prepared from the mixture.

Sample D1 was kept at room temperature for four

hours before it was extruded, with no maturing step.

Sample D2 was subjected to a maturing step of two days at 40°C and then extruded.

Sample D3 was subjected to the same maturing step as sample D2, stored at room temperature for four days and then extruded.

The specifications of the extrusion treatment were those set out in example 1.

The particle size range of the spheroids obtained was 1.2 mm to 1.6 mm.

Using the same procedure as example 1, the percentages of active substance released *in vitro* after 0.5 hour, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours and 8 hours were determined.

The values obtained are set out in Table II.

TABLE II

H	Percentage of active substance released in the case of the samples		
	D1	D2	D3
0.5 hour	25.8	11.4	9.5
1 hour	40.0	23.5	19.0
1.5 hours	48.6	34.5	27.7
2 hours	55.8	41.8	35.9
3 hours	64.6	56.1	49.4
4 hours	73.5	65.7	60.2
5 hours	75.5	69.8	67.1
6 hours	76.8	73.7	71.0
7 hours	81.3	77.7	73.2
8 hours	79.9	78.2	75.1

The results set out in Table II show that the active substance release curves stabilised when the mixture from which the spheroids were obtained had been subjected to a

maturing step before extrusion, making it possible to store a mixture of this kind before extrusion.

EXAMPLE 3

This example concerns a multiparticulate tablet with modified release containing sodium diclofenac as the active substance.

The following powder mixture was prepared for the extrusion step:

- DFC: 40 wt%,
- EC N7NF: 52 wt%,
- DEP: 8 wt%, and
- E110 colouring agent: 0.2 wt%.

The powder mixture was extruded using a single-screw extruder.

The extrusion parameters were as follows:

- temperature of the kneading area and the die: 130°C to 170°C,
- screw speed: 50 rpm,
- pressure in the kneading area: 25 bars to 70 bars,
- chopping tool rotation speed: 746 rpm, and
- die orifice diameter: 1 mm.

The spheroids obtained were used to prepare multiparticulate tablets containing a 100 mg dose of DFC.

The spheroids were first coated.

For this purpose, the spheroids were placed in a turbine.

A binder consisting of an alcohol solution of PVP K30 polyvinyl pyrrolidone sold by BASF was first applied to them.

KOLLIDON CLM (trade mark) disintegrating agent sold by BASF was then applied to the spheroids treated in the above manner. Three samples of spheroids were prepared to which 10 wt%, 15 wt% and 20 wt% of the disintegrating agent relative to the mass of the spheroids were respectively applied.

Multiparticulate tablets were prepared from the three samples of spheroids obtained in this way, and from a sample of uncoated spheroids, by compression in a SVIAC PR 6 (trade mark) rotary compression machine sold by SVIAC, using bevelled punches with a diameter of 10 mm.

The following were determined for the tablets obtained in this way:

- the average mass,
- the thickness,
- the hardness,
- the friability, and
- the disintegration time (as per the 1997 European Pharmacopoeia, Section 2.9.1).

The values obtained in this way are set out in Table III, which also shows the theoretical mass and quantity of active material per gram of spheroids (titre).

TABLE III

	Uncoated spheroids	10% coated spheroids	15% coated spheroids	20% coated spheroids
Titre	411.9 mg/g	382.6 mg/g	363.3 mg/g	343.0 mg/g
Theoretical mass	242.78 mg	261.37 mg	275.25 mg	291.55 mg
Average mass	242.9 mg	255.2 mg	276.33 mg	294.83 mg
C.V. mass	2.43%	2.31%	1.90%	2.14%
Hardness	45.8 N	41.9 N	39.4 N	37.8 N
Thickness	3.15 mm	3.21 mm	3.53 mm	3.86 mm
Friability	0.02%	0.55%	0.18%	0.36%
Disintegration time	> 15 min	6 min 40 s	7 min 40 s	12 min 30 s

The results set out in Table III show that the disintegration speed of the tablets increased with the proportion of disintegrating agent in the coating.

The required disintegration speed could be obtained with less than 20% disintegrating agent.

EXAMPLE 4

This example concerns a multiparticulate tablet with modified release including pseudoephedrine as the active substance.

The following mixture was prepared:

- Pseudoephedrine: 40 wt%,
- EC N7NF : 52 wt%, and
- DEP: 8 wt%.

Spheroids were prepared from the above powder mixture using a single-screw extruder and the following extrusion parameters:

- temperature of the extrusion area and the die: 130°C to 170°C,
- screw speed: 72 rpm,

- pressure in the extrusion area: 40 bars to 90 bars,
- chopping tool rotation speed: 700 rpm, and
- die orifice diameter: 1 mm.

The spheroids obtained were used to prepare multiparticulate tablets containing a 240 mg dose of pseudoephedrine.

The spheroids were first coated.

For this purpose, the spheroids were placed in a turbine.

A binder consisting of an alcohol solution of PVP K30 polyvinyl pyrrolidone sold by BASF was first applied to them.

KOLLIDON CLM (trade mark) disintegrating agent sold by BASF was then applied to the spheroids treated in the above manner. Four samples of spheroids were prepared in this way, to which 5 wt%, 10 wt%, 15 wt% and 20 wt% of disintegrating agent relative to the mass of the spheroid were respectively applied.

Multiparticulate tablets were prepared from the resulting four samples of spheroids, and from a sample of uncoated spheroids, by compression in SVIAC PR 6 (trade mark) rotary compression machine sold by SVIAC, using bevelled punches with a diameter of 14 mm.

The following were determined for the tablets obtained in this way:

- the average mass,
- the thickness,
- the hardness,
- the friability, and
- the disintegration time (as per the 1997 European Pharmacopoeia, Section 2.9.1).

The values obtained in this way are set out in Table IV, which also shows the theoretical mass and quantity of active material per gram of spheroids (titre).

TABLE IV

	Uncoated spheroids	5% coated spheroids	10% coated spheroids	15% coated spheroids	20% coated spheroids
Titre	384.6 mg/g	354.8 mg/g	332.4 mg/g	322.5 mg/g	308.2 mg/g
Theoretical mass	624.02 mg	676.44 mg	722.02 mg	744.19 mg	778.72 mg
Average mass	622.5 mg	683.4 mg	729.0 mg	744.3 mg	771.9 mg
C.V. mass	1.37%	1.21%	1.17%	1.36%	1.18%
Hardness	41.2 N	41.1 N	39.5 N	28.1 N	37.5 N
Thickness	4.82 mm	5.08 mm	5.28 mm	5.55 mm	5.66 mm
Friability	0.02%	0.01%	0.21%	2 cp cracked	4 cp cracked
Disintegration time	> 15 min	4 min 07 s	13 min 27 s	8 min 58 s	> 15 min

The results set out in Table IV show that the disintegration speed of the tablet increased with the proportion of disintegrating agent in the coating, except for the sample with 15 wt% disintegrating agent, which was weaker from the point of view of its hardness.

The required disintegration speed could be obtained with approximately 10% disintegrating agent.

EXAMPLE 5

This example concerns a multiparticulate tablet with modified release containing sodium diclofenac as the active substance.

The following powder mixture was prepared for the extrusion step:

- DFC: 40 wt%,
- EC N7NF: 52 wt%, and
- DEP: 8 wt%.

The powder mixture was extruded using a semi-industrial single-screw extruder.

The extrusion parameters were as follows:

- temperature in the kneading area and the die: 130°C to 170°C,
- screw speed: 50 rpm,
- pressure in the kneading area: 150 bars to 190 bars,
- chopping tool rotation speed: 7 000 rpm to 8 000 rpm, and
- die orifice diameter: 1 mm.

The spheroids obtained were used to prepare multiparticulate tablets containing a 100 mg dose of DFC.

The spheroids were first coated.

For this purpose, the spheroids were placed in a turbine.

A binder consisting of a solution in alcohol of PVP K30 polyvinyl pyrrolidone sold by BASF was first applied to them.

10 wt% relative to the mass of the spheroids of KOLLIDON CLM (trade mark) disintegrating agent sold by BASF was then applied to the spheroids treated in the above manner.

Multiparticulate tablets were prepared from the resulting spheroids by compression in a SVIAC PR 6 (trade mark) rotary compression machine sold by SVIAC, using flat punches 10 mm in diameter.

The parameters determined for the tablets obtained in this way are set out in Table V.

TABLE V

Parameter	Multiparticulate tablet of the invention containing a 100 mg dose of DFC
Titre (mg/g)	357.9
Average mass (mg)	279.4 ± 3.6
Hardness (N)	45.10 ± 5.63
Thickness (mm)	3.58 ± 0.03
Friability (%)	0.09
Disintegration time	9 min 44 s

The tablets were subjected to pharmacokinetic trials in six healthy subjects.

Table VI below sets out the results for the principal pharmacokinetic parameters observed in healthy subjects after administering a multiparticulate DFC tablet containing a 100 mg dose of active substance:

- tmax (h): the time in hours after which the concentration of active principle in the serum reached a maximum,
- Cmax (µg/l): the value of the maximum active principle concentration reached at tmax, expressed in µg of active principle per litre of serum, and
- 0-12 hours AUC (µg.h/l): the area under the curve of the active principle concentration in the serum as a function of time up to the last sample taken, i.e. over a period of 12 hours.

TABLE VI

Parameter	Multiparticulate tablet of the invention containing a 100 mg dose of DFC
Tmax (h)	1.25
Cmax (µg/l)	372 ± 58
0-12 AUC hours (µg.h/l)	1 176 ± 163

The results set out in Table VI confirm that disintegration of the tablet followed by dissolution and absorption of the sodium diclofenac contained in the spheroids occurred in the upper part of the digestive tract of healthy adult subjects. The low variation between subjects indicated the good quality of the DFC formulation of the invention.

CLAIMS

1. Multiparticulate pharmaceutical form, in particular multiparticulate tablet, characterised in that it consists of a plurality of particles, preferably spheroids having a coating based on at least one disintegrating agent and at least one binding agent and optionally at least one active substance and consolidated with one another by compression, said particles or spheroids in which an active substance is distributed within a thermoplastics material having been obtained by hot extrusion without solvent of a mixture of the active substance with the thermoplastics material and chopping the filament or extrudate leaving the extrusion die.

2. Particles, preferably spheroidal particles, characterised in that they are the result of chopping a filament or extrudate obtained by hot extrusion without a solvent of a mixture of an active substance and a thermoplastics material and coating the particles obtained by chopping with a coating including at least one disintegrating agent and possibly including a binding agent and optionally an active substance.

3. Method of making particles, in particular spheroids with a constant diameter in the range from 0.5 mm to 2 mm, including an active substance and having a controlled and predetermined active substance release curve, and which includes successively:

- a step of selecting an active substance and a thermoplastics material, including at least one polymer excipient and at least one plasticiser,
- a step of mixing the active substance and the thermoplastics material,
- a step of extruding the mixture without solvent at a controlled temperature to produce at least one extruded filament or extrudate,

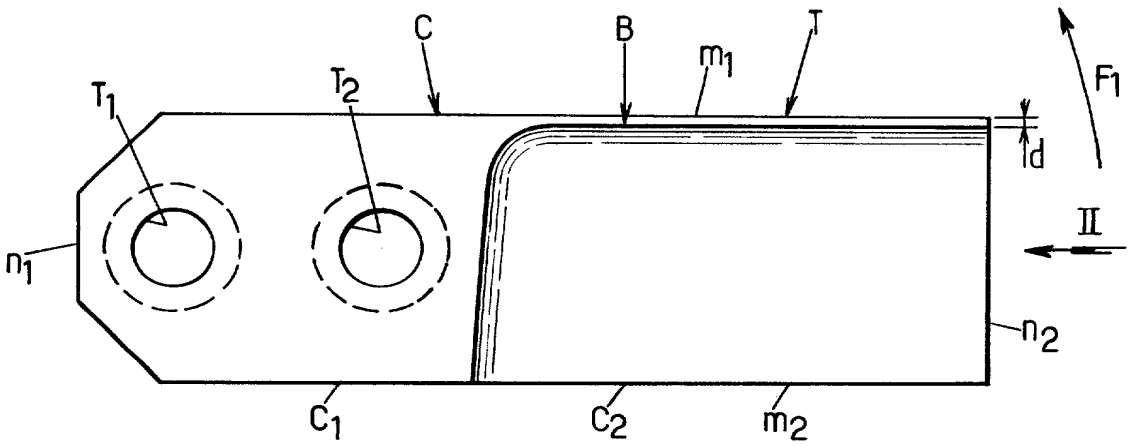
- a step of chopping the extrudate into particles, characterised in that it includes a step of maturing the mixture of the active substance and the thermoplastics material before extrusion at a temperature and for a time chosen according to the characteristics of the intended active principle release curve and respectively in the range from 20°C to 70°C and in the range from 30 minutes to 150 hours, whereby it becomes possible to store the mixture of the active substance and the thermoplastics material for up to 7 days before extruding it and to increase the quantity of active substance for a given release curve without increasing the volume of the tablet.

4. Plant for making spheroids according to claim 2, characterised in that it comprises an extruder having at the exit from the extrusion die a tool for chopping the extruded filament or extrudate equipped with cutters having the shape shown in figures 1 and 2.

ABSTRACT

The invention concerns a multiparticulate pharmaceutical form, in particular multiparticulate tablet, characterised in that it consists of a plurality of particles, preferably spheroids comprising a coating based on at least a disintegrating agent and at least a binding agent and optionally at least an active substance integrated with one another by compression, said particles or spheroids wherein the active substance is distributed within a thermoplastics material having been obtained by hot extrusion without solvent of a mixture of the active substance with the thermoplastics material and cutting up the filament or extrudate leaving the extrusion die.

FIG.1.



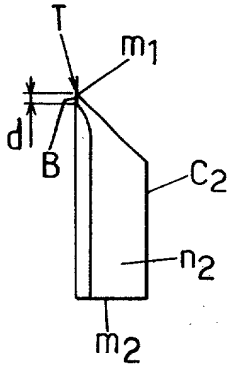


FIG.2.

DECLARATION FOR PATENT APPLICATION

Docket Number (optional)
P1047/20008

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME.

the specification of which

is attached hereto unless the following box is checked:

[X] Was filed on October 6,1999 as United States Application Number or PCT International Application Number 09/402,564 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
97 04234 (number)	FRANCE (Country)	7th April 1997 (Day/Month/Year Filed)	[X] Yes [ ] No
(number)	(Country)	(Day/Month/Year Filed)	[ ] Yes [ ] No

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application (s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international date of this application.

FR98/00697 (Application Number)	7th April 1998 (Filing Date)	(Status-patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status-patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Alan H. Bernstein (Registration No. 19,315); Stanley H. Cohen (Registration No. 20,235); Manny D. Pokotilow (Registration No. 22,492); Barry A. Stein (Registration No. 25,257); Martin L. Faigus (Registration No. 24,364); Eric S. Marzluf (Registration No. 27,454); Robert S. Silver (Registration No. 35,681); Scott M. Slomowitz (Registration No. 39,032) and Michael J. Berkowitz (Registration No. 39,607) care of Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., 12th Floor, Seven Penn Center, 1635 Market Street, Philadelphia, Pennsylvania 19103-2212, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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DECLARATION FOR USA PATENT APPLICATION
(including Design and National Stage PCT)

ADDITIONAL INFORMATION SHEET 1
(use as required)

3-DD

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PATENT
Attorney Docket: P1047/20008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINATION OPERATION

Applicants	:	LOUVEL, Pascal Claude Michel, et al.
Serial No.	:	09/402,564
Filed	:	October 6, 1999
Based on	:	PCT/FR98/00697, filed April 7, 1998
For	:	MULTIPARTICULATE PHARMACEUTICAL FORM, PARTICLES CONSTITUTING IT, METHOD AND PLANT FOR MAKING SAME

FEE VALUE ACCOUNTABILITY
DEPOSIT ACCOUNT NO.
03 0075

FEE CODE	VALUE FURNISHED
154	130.00

SUBMISSION OF DECLARATION FOR PATENT APPLICATION

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (copy attached), mailed from U.S. Patent and Trademark Office on December 9, 1999, Applicants enclose an executed DECLARATION FOR PATENT APPLICATION.

04/07/2000 WCLAYBRO 00000034 030075 09402564
01 FC:154 130.00 CH

The United States Patent and Trademark Office is authorized to charge counsel's Deposit Account No. 03-0075 the sum of One Hundred Thirty Dollars ($130.00),or any other fee as the surcharge appropriate herein. A duplicate copy of this document is enclosed herewith.

04/07/2000 WCLAYBRO 00000034 030075 09402564
02 FC:115

We also enclose an Petition for Extension of Time, in duplicate, in order to permit the timely filing of the Declaration.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN, COHEN & POKOTILOW, LTD.

By_____

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CERTIFICATE OF MAILING

I hereby certify that the foregoing SUBMISSION OF DECLARATION FOR PATENT APPLICATION, in duplicate, and attached Declaration for Patent Application re application Serial No. 09/402,564, are being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Box PCT, Assistant Commissioner for Patents, Washington, D.C. 20231, this 24th day of January, 2000.

_____

Robert S. Silver